REMARKS

No amendments to the claims have been made as a result of this amendment. Accordingly, claims 2, 3, 36-45 are currently pending.

Applicants wish to thank Examiner Yu for the courtesy of a telephone interview on November 20, 2003 with applicants' representatives, Irving N. Feit and the undersigned.

In the Office Action, claims 2, 3 36-45 were rejected under 35 U.S.C. §112, first paragraph allegedly for lack of enablement. The examiner states that to obviate the rejection, "applicant is requested to point out in the specification which specific disease could be treated by inhibiting thrombospondin binding protein (TSP) and any *in vivo* model."

Applicants advised Examiner Yu that the specification at page 6 discloses the treatment of cardiovascular disease and wound healing in accordance with the claimed invention. Also, applicants wish to point out to the examiner that other conditions are further disclosed in the specification (see last paragraph of page 17).

The examiner then inquired whether there was any working *in vivo* examples demonstrating efficacy of the claimed compositions. Applicants responded by directing the examiner's attention to the *in vivo* experiment at the bottom of page 48 to page 49 of the specification. There, the specification discloses two *in vivo* models demonstrating that histidine-rich glycoprotein (HRGP) inhibits the anti-angiogenic effect of TSP in mice.

The examiner indicated during the telephone interview that, in her opinion, the *in vivo* experiments disclosed in the specification were insufficient to obviate the rejection. The *in vivo* experiments demonstrated inhibition of the anti-angiogenic effect of TSP by HRGP. The examiner contends that demonstration of inhibition of the anti-angiogenic effect of TSP by HRGP does not necessarily mean that the composition is useful for treating a disease or

condition.

Applicants respectfully disagreed with the examiner. Applicants argued it is not a requirement to demonstrate an *in vivo* disease model, and that the *in vivo* efficacy experiments demonstrating promotion of angiogenesis on page 48 and 49 of the specification should be sufficient to obviate the rejection. In addition, applicants pointed out to the examiner that it is widely accepted that promotion of angiogenesis would be beneficial in promoting, for example, wound healing.

The examiner responded by indicating that claims directed to a pharmaceutical composition have to be effective in treating a disease or condition. The examiner then stated that without a working disease model, she did not consider the claimed invention to be enabled. The examiner then indicated that data supporting *in vivo* efficacy in a disease/condition model would obviate the rejection.

Applicants continue to disagree that the data the examiner requires is necessary. Merely to expedite prosecution, applicants advised Examiner Yu that *in vivo* wound healing data would be submitted to obviate the alleged lack of enablement rejection (see Interview Summary sheet dated November 21, 2003).

Accordingly, enclosed herewith is a Declaration under 37 C.F.R. §1.132 executed by Dr. Roy L. Silverstein, a co-inventor of the claimed invention. In the Declaration, Dr. Silverstein states that experiments were conducted under his direct supervision and control for the purpose of demonstrating increase cutaneous angiogenesis and accelerated wound closure in transgenic mice expressing histidine-rich glycoprotein. The experiments conducted are described in Exhibit 1.

Briefly, transgenic mice over-expressing HRGP were generated by transfecting normal mice with additional full length murine HRGP genes driven by the keratin 14 (K14) promoter in

basal keratinocytes. Two transgenic lines were established, the Tg 1 and the Tg 19 transgenic mouse line. The Tg 1 mouse line contained seven copies of the transgene and the Tg 19 contained twelve copies. Analysis of the skin extracts of these transgenic mice demonstrated a greater than ten-fold increase in HRGP than control (wild-type) mice. Analysis of the blood vessels of whole mounts of the ears also demonstrated an increase in vascular tortuosity and branching in the transgenic mice compared to control mice. Further, immunohistochemical staining of skin sections from wild-type and transgenic mice with an antibody against the endothelial cell marker PECAM (CD31) showed a greater number of CD31 positive cells in the transgenic mice than in the wild-type control mice. See paragraph 2 of the Silverstein Declaration.

Dr. Silverstein attests that the observed increase in vascular tortuosity and branching, and the greater number of CD31 positive cells, in the transgenic mice than in the wild-type control mice indicates that the increased expression of HRGP in the skin of transgenic mice leads to increased blood vessel formation (e.g., angiogenesis). See paragraph 3 of the Silverstein Declaration.

Dr. Silverstein utilized the two transgenic mouse lines (Tg 1 and Tg 19) to examine the effect of increased expression of HRGP in a wound model *in vivo*. In one wound-healing model, described in exhibit 1, the mice were subjected to full thickness punch wounds. The time to wound closure was measured. Dr. Silverstein attests that in this model, one of the transgenic mouse lines (Tg 1) showed accelerated wound closure compared to control mice without the transgene. The other transgenic mouse line (Tg 19) did not. The Tg 1 transgenic mouse line expressed more HRGP than both the Tg 19 transgenic mouse line and the control mice. See paragraph 4 of the Silverstein Declaration.

Another *in vivo* model of wound healing was also utilized to study the effect of increased expression of HRGP. The experiment is also described in exhibit 1.

Briefly, mice were implanted subcutaneously with polyvinyl alcohol sponges. Dr. Silverstein attests that analysis of the sponges demonstrated a greater amount of vascularization in the wound granulation tissue of the Tg 1 transgenic mouse line than in the control mice. In addition, Dr. Silverstein states that a greater number of fine fibrovascular networks was detected in the transgenic mice compared to the control mice. See paragraph 5 of the Silverstein Declaration.

Dr. Silverstein further declares that results similar to those observed for Tg 1 transgenic mouse line described above, were also observed in the Tg 19 transgenic mouse line. Specifically, Dr. Silverstein attests that, although to a lesser degree than that of the Tg 1 transgenic mouns line, analysis of the sponges also showed a greater amount of vascularian in the wound granulation tissue of the Tg 19 transgenic mouse line than in the control mice. See paragraph 6 of the Silverstein Declaration.

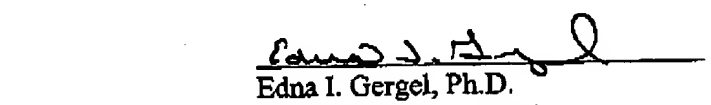
Accordingly, Dr. Silverstein attests that the above results demonstrate that over-expression of HRGP promotes angiogenesis and promotes wound healing. See paragraph 7 of the Silverstein Declaration.

Therefore, applicants have complied with the examiner's request that applicants provide evidence demonstrating *in vivo* efficacy in a disease model. Thus, applicants respectfully request that the rejection be withdrawn.

In view of the above remarks and Rule 132 Declaration of Dr. Silverstein, allowance of pending claims 2, 3, 36-45 is earnestly requested. If the examiner has any questions regarding

this amendment, she is respectfully requested to contact the undersigned at the telephone number listed below.

Respectfully submitted,



Edna I. Gergel, Ph.D.
Registration No. 50,819
Agent for Applicants

HOFFMANN & BARON, LLP
6900 Jericho Turnpike
Syosset, New York 11791
Tel. (516) 822-3550
Fax. (516) 822-3582

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